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JPRS: 42

21 November 1960

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DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS

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-USSR-

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JPRS: 4207

CSO: 1126-S/c

THE EFFECT OF CERTAIN HYPOTONIC SUBSTANCES ON THE DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS.

-USSR-

[Following is the translation of an article entitled "Vliyaniye Nekotorykh Gipotenzivnykh Veschestv Na Razvitiye Eksperimental'nogo Ateroskleroza" (English version above) by N.A. Novikova in Patologicheskaya Fiziologiya i Eksperimental'naya Terapiya (Pathological Physiology and Experimental Therapy), Vol IV, No 4, Moscow 1960, pages 42-46.]

There are indications in the literature of the frequent combination of hypertonic malady and atherosclerosis.

Many clinical observers have noted that in the initial stages of hypertonic ailment, concurrent atherosclerosis is much more serious (4, 6, 8-11, 20). This is reaffirmed by experimental evidence (1, 16, 21). Certain pharmaceuticals which increase arterial pressure (adrenalin, ephedrin, desoxycorticosterone acetate) also increase the development of experimental atherosclerosis (19, 21, 24). It has been shown that poisons which contract blood vessels (vasopressin, adrenalin, lead) bring on "sclerosed blood vessels" after a protracted period of application. Substances which expand the blood vessels (histamine, nitrates) have an "antisclerotic" action (23).

Some substances which decrease arterial pressure by means of their effect on vascular walls (papaverine, nitroglycerine) retard the development of experimental atherosclerosis (7). Narcotic substances have the same effect, producing a decrease in arterial pressure (2, 13, 18).

The data now available in the published materials on this subject regarding the effect of a hypotonic substances on the development of atherosclerosis by no means exhaust this important question. Especially interesting is the study of the effect on the course of atherosclerosis of hypotonic substances which are frequently used in treat-

ment of hypertonic ailments. Hexone, the ganglion-blocking substance, belongs in this category, since it is one of the most potent hypotonic remedies, and is being used ever more widely in the treatment of hypertonic ailments. This also is true of dibasol.

The present work deals with the influence of hexone and dibasol on the development of experimental atherosclerosis. We found no data on this in the available literature.

The experiments were conducted with seventy male rabbits weighing from two to three and five tenths kilograms. Atherosclerosis was induced with N.M. Anichkov's method. Two tenths gram per kilogram weight of cholesterol in a 5% oily solution were introduced daily through a stomach probe for four months.

Hexone was used in the form of the benzol sulphate salt (benzohexone):



Benzohexone is less toxic and stronger in its hypotonic action than iodohexone (5, unpublished data of P.P. Denisenko). Benzohexone was introduced subcutaneously in daily doses of two to ten mg/kg for a period of four months. These doses were determined by the fact that in rats and in mice, thyroid function is increased by two mg/kg doses of methylsulphate salt of hexone, and decreased by ten mg/kg doses (15). Changes in thyroid functions can have a significant effect on the development of atherosclerosis (14, 17, 22). In the control experiments, benzohexone lowered the blood pressure by 20%-40%.

Dibasol, i.e. hydrogen chloride salt of 2-benzyl-benzimidazole:



was used daily for four months in 10mg/kg doses administered subcutaneously, since in this dosage a more marked lowering of arterial pressure was produced (12).

Using the method of Neuschloss, the level of cholesterol in the serum of the experimental animals was checked once a month, as was the phospho-lipid (lecithin) level, with the use of the Fiske-Subarroy method. The cholesterol/lecithin index was calculated. At the end of the four month period, the animals were killed.

Atherosclerotic changes in the aorta were determined after macroscopic staining with cerasin red, and the degree of affection was denoted by plus marks (+ slight atherosclerosis, ++ moderate, +++ acute, ++++ extremely acute). [Note] In evaluating the intensity of atheroscler-

otic affection in the aorta, we had the very kind help of our scientific colleague, E.E. Kikayon of the department of pathological anatomy of the Institute of Experimental Medicine.)

In noting the changes of total cholesterol and lecithin levels in the blood, and in the cholesterol/lecithin index, we calculated the average for one month in each experimental group. The averages derived from these data during four months of observation were then subjected to statistical calculations.

Four series of experiments were conducted.

In the first series, nineteen rabbits received cholesterol and served as a control. In the second series, nine experimental rabbits received 2 mg/kg of hexone together with cholesterol. Six of the control animals received 2 mg/kg of hexone only. In the third series, seven experimental animals received both cholesterol and 10 mg/kg of hexone at the same time, while ten controls received hexone only in a 10 mg/kg dose. The fourth series of experiments was done with thirteen rabbits which received dibasol and hexone simultaneously, while six control animals received dibasol only.

In all the animals the introduction of cholesterol produced an increase in the cholesterol and lecithin levels in the blood serum, and an increase in the cholesterol/lecithin index.

In rabbits which received hexone together with cholesterol, the level of the latter had a slower increment than in the controls which received cholesterol alone. This was not noted when cholesterol and dibasol were introduced simultaneously (Table 1).

Before experimentation the level of cholesterol in the blood serum averaged 51.6 ± 2.5 mg%; lecithin level, 89.2 ± 4.7 mg%; the cholesterol/lecithin index reached 0.63 ± 0.03 (fig 1 and 2). As a result of the four month observation, it was found that the over-all cholesterol level in the animals of the control series receiving cholesterol only, increased and reached an average of 530 ± 29.4 mg%. Simultaneously, the lecithin level also increased, but its rate of increment was slower than that of cholesterol. The lecithin increase averaged 252 ± 14.5 mg%. The cholesterol/lecithin index increased correspondingly to 2.24 ± 0.13 .

In the group of animals receiving cholesterol and two mg/kg of hexone simultaneously, there was a slight retarding in the rate of increase of over-all cholesterol level. The average increment of cholesterol was 408 ± 54.2 mg%; lecithin level, 226.3 ± 28.4 mg%; and the corresponding

cholesterol/lecithin index fell to 1.9 ± 0.28 . The most marked inhibition of the increase of cholesterol level was noted in that group of rabbits which received 10 mg/kg doses of hexone simultaneously with cholesterol. Here, the cholesterol level was 314.5 ± 50 mg%; lecithin level, 187.9 ± 23.3 mg%; the corresponding cholesterol/lecithin index dropped to 1.7 ± 0.2 . Simultaneous introduction of dibasol and cholesterol caused a slightly raised cholesterol level to go up to 559.8 ± 36.1 mg%. The lecithin level likewise, reached higher figures than in the control -- 304 ± 16 mg%. But the cholesterol/lecithin index was lower than in the control animals, down to 1.8 ± 0.07 .

The introduction of hexone and dibasol into untouched animals did not produce significant level changes in cholesterol or lecithin, or in the cholesterol/lecithin index (see Table 1, fig 1 and 2).

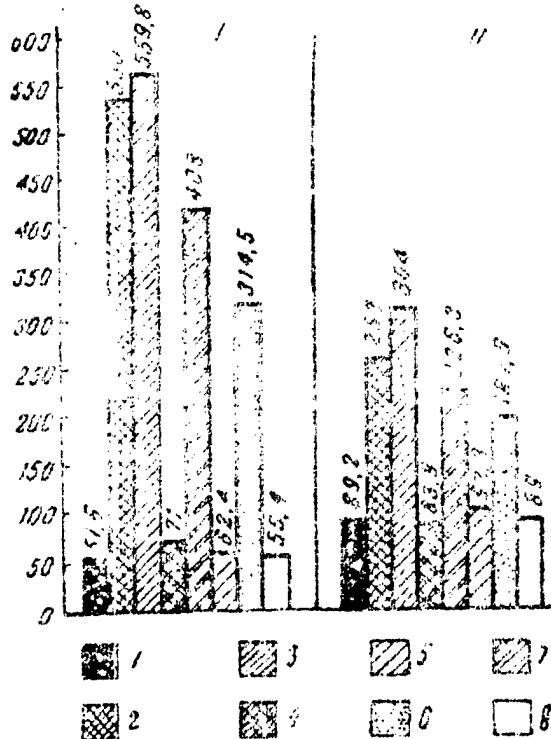


Fig 1. legend. Cholesterol level (I) and lecithin level (II) in milligram-percent in rabbit blood serum (averages during four months' observation) 1) in normal (before experiment) with introduction of: 2) 0.2 gm/kg



Fig 2 legend. Cholesterol/lecithin index (averages during four months of observation). Legend same as in fig 1.

Fig 1. legend (cont'd).
 cholesterol; 3- 0.2 gm/kg cholesterol and 10 mg/kg dibasol; 4- 10 mg/kg dibasol; 5- 0.2 gm/kg cholesterol and 2 mg/kg hexone; 6- 2 mg/kg hexone; 7- cholesterol and 10 mg/kg hexone; 8- 10 mg/kg hexone.

Table 1. Cholesterol and lecithin level in blood serum and index of cholesterol/lecithin (averages during one month of observation)

A) Groups of rabbits, receiving B) before experiment C) cholesterol (in mg%) D) lecithin (in mg%) E) index F) first month G) second month H) third month J) fourth month K) cholesterol L) cholesterol & hexone 2 mg/kg M) Hexone 2 mg/kg N) cholesterol & hexone 10 mg/kg O) hexone 10 mg/kg P) cholesterol & dibasol 10mg/kg Q) dibasol 10 mg/kg

Группы кроликов, подвергнутые	До опыта		После опыта		Бород. масса		Третий месяц		Четвертый месяц						
	ЧОЛЕСТЕРИН (в мг%)	ЛЕЦИТИН (в мг%)													
К) Холестерин и гексон 2 мг/кг	52,5	97,8	50,5	194,5	1,64	551,4	214,5	2,93	630,8	305,9	2,4	595,6	345,6	1,98	
Л) Гексон 2 мг/кг	49,1	100,7	0,4	247,1	1,14	400,0	188,1	2,15	481	267,1	1,8	418,5	268,4	1,45	
М) Гексон 10 мг/кг	63,4	66,5	0,9	46,8	125,2	0,4	42,8	76,9	66,6	64,2	0,78	85,6	59,9	0,86	
О) Холестерин и гексон 10 мг/кг	57,4	105,5	0,54	218,5	2,67	112	280	122,4	2,1	344,2	180,1	1,6	485,2	249,2	2
П) Холестерин и гексон 10 мг/кг	51,8	90,5	0,59	46,6	86,8	0,53	60	108	0,55	53,8	76,6	0,7	58,7	82,6	0,72
Q) Холестерин и дипазол 10 мг/кг	45,8	63,1	0,65	43,1	215,2	1,59	556,9	308,8	1,84	600	349,9	1,69	727,6	344	2,14
С) Дипазол 10 мг/кг	48,3	71,9	0,67	70	85,1	0,8	64	93,3	0,86	70	76,3	0,76	80	63,2	0,92

Группы кроликов, подвергнутые

Table 2

У кроликов, полу- чивших	Кролики												
	1	2	3	4	5	6	7	8	9	10	11	12	13
④ Холестерин 0.2 г/кг	++++	++++	++++	+++	+++	+++	+++	+++	+++	+++	+		
⑤ Холестерин и гексоний 2 мг/кг	++++	+++	++	+	+	+	+						
Холестерин и гексоний 10 мг/кг	+++	+++	++	+	+	-	-						
Холестерин и дубазол 10 мг/кг	+++	+++	++	++	++	++	+	+	++	+	+	+	-
⑥ Гексоний 2 мг/кг	-	-	-	-	-	-	-						
⑦ Гексоний 10 мг/кг	-	-	-	-	-	-	-	-	-	-			
⑧ Дубазол 10 мг/кг	-	-	-	-	-	-	-						

Table 2. Degree of atherosclerotic impairment of the aorta

A) In rabbits receiving B) rabbits C) traces D) cholesterol 0.2 g/kg E) Cholesterol & hexone 2mg/kg F)cholesterol & hexone 10 mg/kg G)cholesterol & dibasol 10 mg/kg H)hexone 2 mg/kg J)hexone 10 mg/kg K)dibasol 10 mg/kg

The use of hexone in two and 10 mg/kg doses, and dibasol in 10 mg/kg doses, serves as a brake to the development of atherosclerotic aortal changes in animals receiving cholesterol (Table 2).

Thus, under experimental conditions hexone, especially in heavy doses, somewhat lowered the alimentary hypercholesterolemia and tended to inhibit the rate of development of experimental atherosclerosis.

Dibasol did not inhibit the development of alimentary hypercholesterolemia. However, in rabbits receiving dibasol, the aortic walls showed less marked atherosclerotic changes than did the controls. It may be that the observed inhibiting effect of hexone and dibasol on the development of experimental atherosclerosis is connected

with the lowering of arterial pressure under the influence of these substances. This agrees with present indications in the literature regarding the negative effect of hypotonic substances in experimental development of atherosclerosis (7). At the same time, the difference in the effects of hexone and dibasol on hypercholesterolemia indicate that in the inhibition of atherosclerosis by the ganglion-blocking hexone there are other factors besides the lowering of arterial pressure. Since hexone can variously affect metabolism, depending on the health of the organism (3), it may be that hexone's inhibition of alimentary cholesterolemia is related directly or indirectly to its effect on cholesterol metabolism.

CONCLUSIONS

1. In normal animals, benzohexone in two and ten mg/kg dosages, and dibasol in ten mg/kg doses, do not significantly influence the total cholesterol and lecithin level in the blood. The cholesterol/lecithin index is unchanged.
2. Benzohexone inhibits the development of experimental hypercholesterolemia. This inhibitory effect is increased with the increase in dosage from two to ten mg/kg.
3. In ten mg/kg doses, dibasol does not inhibit the experimental development of hypercholesterolemia.
4. Benzohexone in two and ten mg/kg doses, and dibasol in ten mg/kg doses inhibit the development of experimental atherosclerosis.

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